Functional Impairment in Miro Degradation and Mitophagy Is a Shared Feature in Familial and Sporadic Parkinson's Disease.

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Public Summary:
Using iPSC-derived neurons and other models, Hsieh et al. uncover a defect in clearance of damaged mitochondria in Parkinson's disease. They show that in mutant cells, the mitochondrial outer membrane protein Miro is stabilized and remains on damaged mitochondria for longer than normal, prolonging active transport and inhibiting mitochondrial degradation.

Scientific Abstract:
Mitochondrial movements are tightly controlled to maintain energy homeostasis and prevent oxidative stress. Miro is an outer mitochondrial membrane protein that anchors mitochondria to microtubule motors and is removed to stop mitochondrial motility as an early step in the clearance of dysfunctional mitochondria. Here, using human induced pluripotent stem cell (iPSC)-derived neurons and other complementary models, we build on a previous connection of Parkinson's disease (PD)-linked PINK1 and Parkin to Miro by showing that a third PD-related protein, LRRK2, promotes Miro removal by forming a complex with Miro. Pathogenic LRRK2G2019S disrupts this function, delaying the arrest of damaged mitochondria and consequently slowing the initiation of mitophagy. Remarkably, partial reduction of Miro levels in LRRK2G2019S human neuron and Drosophila PD models rescues neurodegeneration. Miro degradation and mitochondrial motility are also impaired in sporadic PD patients. We reveal that prolonged retention of Miro, and the downstream consequences that ensue, may constitute a central component of PD pathogenesis.

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